Wyeth Pharmaceuticals

Wyeth

3276 '04 MAR -9 A9:11

Date: March 8, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0493, Federal Register: November 7, 2003 (Volume 68, Number 216, Page 63109-63110)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the attached comments (attachment 1) on the FDA's draft guidance dated October 2003 on ***Powder Blends and Finished Dosage Units – Stratified in-process Dosage Unit Sampling and Assessment.***

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biologicals and over the counter medications. As such, Wyeth supports the comments submitted by the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Parenteral Drug Association (PDA). We have highlighted a number of points discussed with representatives of these organizations that we believe are of particular importance (attachment 2).

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance, and trusts that the Agency will take these comments into consideration when preparing the final guidance.

Sincerely,

Roy J. Baranello

Roy J. Baranello, Jr.
Assistant Vice President,
Worldwide Regulatory Affairs

2003D-0493 C10

Wyeth

Attachment 1
Wyeth Comments: FDA Guidance
"Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment"

Section	**Guidance Line**	**Comment**	**Rationale**
III.	60-65	Remove definition from Scope	This is a definition and should not be the introductory paragraph of the Scope.
III.	67-72	Move to Introduction	Provides clarity and strengthens the flow of the document by moving this section to the Introduction.
III.	74-86	For clarity, move to line 60 and suggest rewording as follows: Line 74 (new 60): " This guidance suggests procedures to ensure adequate mixing and dosage uniformity via the following steps:" Also suggests adding the following bullet as the first bullet. "Conduct sample blend testing procedures by evaluating appropriate sampling thief design, appropriate sample size and sampling technique	Better defines the purpose of the Guidance Document.
III.	99-101	For clarity, suggest the lines to be reworded as follows: "When using the methods described in this guidance, certain data may reflect trends. We recommend that manufacturers scientifically evaluate how these trends may affect the quality of a product. "	Provides clarity.
IV.	113	Change the word "how" to "procedures".	Provides clarity.
IV.	125-139	Create sub-bullets to distinguish between the different steps. For example, • Develop blend sampling techniques. o Extensively sample the mix in the	Provides clarity. We propose a hierarchy for the first three bullets because of their relationship to each other and the fact that they separate development from the

Section	**Guidance Line**	**Comment**	**Rationale**
		blender and/or intermediate bulk containers (IBC). o Identify appropriate blending time and speed ranges, dead spots in blenders, and locations of segregation in IBCs. Determine sampling errors. o Define the effects of sample size (e.g., 1-10X dosage unit range) while developing a technique capable of measuring the true uniformity of the blend. Sample quantities larger than 3X can be used with adequate scientific justification. Appropriate blend sampling techniques and procedures should be developed for each product with consideration to various designs of blend powder sampling and the physical and chemical properties of the blend components. • Design blend-sampling plans and evaluate them using appropriate statistical analysis. • Quantitatively measure any variability that is present among the samples. Attribute the sample variability to either lack of uniformity of the blend or sampling error. Significant within-location variance in the blend data can be an indication of one factor or a combination of factors such as inadequacy of blend mix, sampling error[9] or agglomeration[10, 11]. Significant between-location variance in the blend data can indicate that the blending operation is inadequate.	blend sampling execution.
IV.B.	158	The purpose of this statement is not clear. We suggest that it be deleted unless it can be clarified.	The use of this definition is not consistent with the definition provided in the document's glossary. This statement is unclear.
IV.B. IV.C.	161 and 183	This section refers to development batches only and may not be the actual process that will be validated. Providing summaries from the early stages (not commercial scale) of	

Section	**Guidance Line**	**Comment**	**Rationale**
		development may not be fully representative. Only data supporting validation should be required.	
IV.B.	168-170	Recommend a specific reference to PAT, for example, by adding "such as PAT" to the end of the sentence on line 170.	Provides clarity of what " alternate state-of –the art methods" means. The sentence implies that PAT could be used.
V & VI	General Comment	Suggest combining Sections V and VI under the proposed heading of " V. Evaluation of Exhibit/Validation Batch Powder Mix Homogeneity".	Both sections refer to Exhibit/Validation batches.
V& VI	General Comment	Subsection numbering would need to be appropriately changed.	Provides continuity with previous comment.
V.	203	We are unsure of what is meant by "uniform volumetric sampling".	Clarification is needed.
V.	224-229	A clarification is needed to explain what indirect sampling means. We may want to add statements recommending when blend sampling is not possible e.g.: Equipment (Blender design issues), Safety issues of sampling from the blender and/or IBC, density of powder bed makes it physically impossible to sample directly.	Definitions of alternate means of sampling may be necessary for clarification for when it may be impossible to directly sample the blend.
VI.	239	Change the word "criteria" to the word "classification".	Provides clarity in describing the actual intent of this document.
VI.A.	250	Add to the statement: "Carefully identify locations throughout the compression or filling operation to sample in-process dosage units, based on results of development studies when available."	Provides clarity.
VI.D.	313-314	We suggest the following clarification be added at the end of the paragraph: "It is acceptable to use 10 locations as long as they include all of the locations shown to potentially have an affect on quality during the assessment."	The USP content uniformity (CU) test requires 10 dosage units for evaluation at stage 1. During routine production exactly 10 locations should be acceptable, since any more than 10 would make evaluation of the USP CU test confusing.
VII.	319-321	Suggest the following wording: " After completing the procedures described above, it is recommended that you evaluate the routine manufacturing batches using the following criteria. "	Provides clarity.

Wyeth

Section	**Guidance Line**	**Comment**	**Rationale**
VII.B.	394-398	If the test results during routine manufacture fail the criteria, we disagree that "you should no longer use the verification testing methods to ensure adequacy of mixing or uniformity of content until you investigate the failure (per 21 CFR 211.192) to establish justified assignable cause(s), take necessary corrective actions and repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures."	Judgment needs to be used to decide what the appropriate action is that should be taken on subsequent batches made during the period that the original failing batch is being investigated. A general statement meant to fit all cases is not appropriate.
VII.B.	398	The guidance should make the same statement that it does on lines 304-305 (but replacing the words "marginally pass" with the words "MCM") to read "The disposition of batches that have failed the MCM criteria is outside the scope of this guidance."	The relevance of this statement seems to be just as true for line 398 as it is for lines 304-305, where the statement is included. We assume it's just an oversight.
VIII	General Comment	Summaries of data will not always be available at time of filing. We suggest that it be submitted only if available.	
Attachment 1	491-503	A company should be allowed to pass blender S1 criteria with n=30 if it fails S1 criteria with n=10 before requiring investigation of original S1 criteria "failure" and determination of whether there is a mixing problem.	S2 should have an acceptance criteria and not just a general requirement to determine if there is a mixing problem. Meeting the S1 blender criteria with n=30 should be a satisfactory demonstration that there is not a mixing problem. If not met at S2, then we believe the investigation is then necessary.

Section	**Guidance Line**	**Comment**	**Rationale**
	General comment	We believe it is not practical to require a new validation for all existing products where the original validation was not performed as stated in the guidance. Some additional guidance is needed. If an existing validation can be shown to be at least as discriminating as the guidance and it meets either the readily pass or marginally pass, we feel that this would be satisfactory justification for using the guidance criteria for routine manufacture. In addition, if we have satisfactory blender test results (as per the guidance document) but, while acceptable, we can't demonstrate that the existing validation data for in-process dosage units is at least as discriminating as that of the guidance, then we feel that that as a worst case, one should be allowed to pick up the routine testing using the MCM sampling and criteria requirements and switch to the SCM criteria after meeting the switching rule criteria for switching	As long as we have demonstrated no mixing problem, this approach would use the more conservative criteria and larger sample size associated with the MCM criteria for routine production until the switching rules would allow switching to the SCM criteria.

Wyeth

Attachment 2

Guidance for Industry
Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
General Comment	The guidance avoids the term 'validation', using less-descriptive titles like "verification of manufacturing criteria". We recommend including the terms 'validation' and 'development' to clarify the purpose of various sections.	The PQRI proposal clearly defines activities that are performed during development (pre-validation) and validation. The reluctance to use the term 'validation' creates a disconnect with the PQRI proposal and makes the draft guidance more difficult to interpret.
General Question	If, through development, we know that reliable blend sampling is unattainable (up to 10x) due to thief error and we have data to prove this, do we still need to pull blend samples during validation or can we skip sampling from the blend in validation and use the Stage 2 dosage unit testing to demonstrate uniformity of blend?	Continuing to utilize a flawed test would not add meaningful data to the Validation exercise. This does not remove the obligation of the firm to use good science to continue the search for a more robust sampling methodology.

Wyeth

Guidance for Industry
Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
58	The following lines are suggested for inclusion in the Scope: "After Readily Passing all validation batches, products that are allowed to meet USP requirements using content uniformity by weight variation are exempted from future routine blend testing requirements."	The PQRI report to FDA recommended the exclusion from the requirements of the guideline those products where the determination of dosage-form uniformity by weight variation is allowed. The former BU draft guidance for ANDA products also excluded these products.
95-97	Remove sentence, " Formulations with extremely low dose and/or high potency may call for more rigorous sampling…units.	Sentence is ambiguous in that it calls for more rigorous sampling, but gives no guidance or reference to how to accomplish these ends.
108	For clarity: Change the section title so that it clarifies that these exercises are Development (pre-validation) procedures. One possibility: "IV. Evaluating Powder Mix and In-Process Stratified Sampling During Process Development"	It is not clear (to all readers) that this section is a separate procedure from that proposed in Section V. A title and purpose statement will help clarify the reason for the difference in sampling scheme and lack of acceptance criteria.

Guidance for Industry
Powder Blends and Finished Dosage
Units — Stratified In-Process Dosage
Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
123	Add a 'purpose statement' to this line. For example: "As part of development, we recommend that you assess critical events in the blend process and determine appropriate sampling techniques for demonstrating a validated blend process. As part of this evaluation, we recommend the following procedures."	Clarity, to help others understand the importance of the section.
146	Add a 'purpose statement' to this line. For example: "Prior to validation, we recommend that you assess the in-process dosage unit data to identify locations throughout the compression/filling operation that have a higher risk of producing failing finished product uniformity of content results and to identify trends due to segregation or poor powder mix. We recommend the following steps:"	Clarity, to help others understand the importance of the section.
160-161	Change lines 160-161 to read "Prepare a summary of the data (and analysis), identifying the significant events in the manufacturing process that may impact blending and from this, identify the stratified sampling that may be used to verify powder mix uniformity. We..."	To clarify purpose and prevent some confusion over the statistical use of the term 'correlate'.
172-185	Reformat for clarity: Move this section under the topic of Section VI, with the additional option that if this verification has previously been completed in development, that it is not necessary to repeat the evaluation	Most companies will use the extended testing during validation to compare in-process to finished product, in order to obtain better estimates. During development, it may not be practical to obtain a sufficient amount of data to demonstrate equivalency or 'correlation' between final and in-process product.

Guidance for Industry
Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
174	Add a purpose statement to this line: "In order to use in-process samples to fulfill the compendial uniformity of dosage units requirement for finished products, we recommend the following steps:"	It is currently unclear why this section is important.
216 (revised)	The following revision of the revision is suggested: If samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. Assay the remaining replicate blend samples. To aid in investigating the cause of failure, dosage form samples (seven from at least 20 locations) may be analyzed. These samples should have been obtained following the procedures described in Section VI, Verification of Manufacturing Criteria. If the cause of failure is identified as a mixing problem, we recommend that you do not proceed further with implementation of the methods described in this guidance until a new mixing procedure is developed. If the cause of failure is not because of mixing, but is attributed to sampling error, or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form data as described in Section VI.	Attachment 1 needs to be slightly revised to conform to this change in wording. The box containing the text, "Assay at least seven dosage units per each location, weight correct each result" should be moved to be just under the box containing the text, "Assay 2nd and 3rd blend samples from each location"

Guidance for Industry
Powder Blends and Finished Dosage
Units — Stratified In-Process Dosage
Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
224-233	Move section under V. 1. After the word risk in line 224 add "or physically impractical (example, large V-Blender.	This section seems to describe the general practice of sampling. It would flow better if placed as suggested, where the guidance discusses locations of sampling. Some blender installations due to size of the blender or room considerations do not lend themselves to safe or practical sampling in the blender. In such cases sampling from drums after discharge may be justified as long as location sequence is maintained.
Amendment line number 260 (new text)	Change to "Conduct an analysis of the dosage unit stratified sampling data to assess the active ingredient distribution throughout the batch (e.g, visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or other forms of a distribution other than bell-shaped should be evaluated."	Actually, a unimodal shape or bell-shape with short tails (high peak of data in the center) is not a 'normal' distribution, but it is a preferred shape when describing batch uniformity. A normal distribution is acceptable, but not required.
273	Change to "For each separate batch, compare the weight-corrected test results to the following criteria:"	Clarification for those not familiar with PQRI proposal
289-291	Change to "If your dosage unit test results fail to meet the criteria for the readily pass classification, compare the weight corrected test results to the following criteria:"	To comply with the Amended line 283, which describes how many to test. Plus, clarify the data are weight corrected for those not familiar with PQRI proposal.

Guidance for Industry
Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
337	In addition to the amendment text, add another bullet: • Previous routine test was per SCM and passed SCM criteria.	3 scenarios to use SCM exist in PQRI document: 1. Validation was readily pass and we are just starting production 2. Routine test method is SCM and we continue this as long as we keep passing 3. Routine method is MCM, but switching rule is met
382	In addition to the amendment text, add another bullet: • Previous routine test used MCM and passed MCM criteria	3 scenarios to use MCM exist in PQRI document: 1. validation was marginally pass and we are just starting production 2. routine test method is MCM and we continue this until we can switch 3. last batch started as SCM, but had to go to MCM to pass
Amendment line number 395 (new text)	Minor changes to last sentence: "That is, to establish justified assignable cause(s), take necessary corrective actions, and if appropriate, repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures."	If a single lot fails SCM and MCM, and the root cause is identified to be due to a deviation from the validated process (say materials were not added in correct order), we do not want to have to go through revalidation of all correlations, just reject lot and put measures in place to prevent reoccurrence. But, if the process is 'broken' and must be fixed, then this all needs to be done
416	(CTD17 3.2.P.3.3). Replace with P.3.4	Drug Product Draft Guidance January 2003 lists controls for critical steps under P.3.4
429	(CTD 3.2.P.4.1) Replace with P.5.1	P.5.1 applies to specifications for drug products
436	(CTD 3.2.P.2.2) Replace with P.2.3	P.2.3 applies to manufacturing process development.

Guidance for Industry
Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

PDA Comments

Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
Revised Attachment 1 flowchart, line 498	Move box "Assay at least 7 dosage units per each location, weight correct each result" (from line 507) up to after box that says "Assay 2nd and 3rd blend samples from each location".	The dosage unit data is generally used as part of the investigation to help correlate blender problems or identify sample bias.
Revised Attachment 1 flowchart, line 508	Replace box that says "Assay at least 7 dosage units per each location, weight correct each result" with box that says "Use dosage units to verify adequacy of powder mix"	Although the results were assayed earlier to help in the blend investigation, now we have identified blend sample error so they must be used to demonstrate uniformity of mix.

PhRMA Comments

Section	**Guidance Line**	**Current Guidance Cross-Reference**	**Comment**	**Rationale**
I	18-23		Include in the introduction that the guidance allows the manufacturer to assess the adequacy of powder mix/drug uniformity by the use of stratified in-process samples instead of continuing to struggle with blend sampling issues, provided that a feasibility assessment is made prior to implementation of the stratified sampling approach.	This key advantage of the guidance should be stated in the beginning of the document.
III	82-83		Change text to "Compare the stratified in-process dosage unit data with the finished dosage unit data to determine whether in-process samples may be used to assess uniformity of content"	Clarity
IV. A.	128		How does the agency expect us to determine sampling errors? Please specify.	Not explained.
VI.D.	308-315		Move Sub-section VI.D to Section VII.	More appropriate to be under ROUTINE MANUFACTURING...rather than under VERIFICATION OF MANUFACTURING CRITERIA
VII. A.2.	348		Add a footnote as follows: (3) weight correct[17] [17]Allow for the option of not weight correcting the stratified unit dose data during routine batch manufacture.	Using non-weight corrected data to pass routine manufacturing criteria is more stringent, but it allows for only one set of calculations to pass both the routine criteria and the content uniformity test
VIII	415		We recommend that you provide the following information, *if available,* in the	Most valuable data would be generated from validation batches which most likely are not made at the time of filing.
VIII	416,429,436		Consolidate all information provided into *single* CTD section-preferably CTD 3.2.P.3.3.	Information is spread over different sections of application and make it

Wyeth

Section	**Guidance Line**	**Current Guidance Cross-Reference**	**Comment**	**Rationale**
				difficult to compile, link and review.
General Comments on multilayer tablets			Indicate how the guidance would be applied to multilayer tablets when actives are in the different layers. Indicate how to evaluate stratified samples of bilayer tablets.	If there are two different assays for the two different actives, one could be in a situation of having to apply SCM for one active and MCM for the other. The acceptance criteria are based on weight corrected data, we need a provision to be able to use non-weight corrected data.
Attachment II	Revised Attachment 2 flowchart		The 4 boxes at the top of the flowchart are confusing to some. We recommend listing the 3 situations that allow you to test SCM and the 3 that allow MCM in a bullet list above the flowchart. Begin the flowchart with the first diamond. Use SCM routine criteria if: 1. validation was readily pass and you are just starting production, or 2. routine test for the previous batch was SCM and it passed SCM criteria, or 3. routine test for the previous batch was MCM, but switching rule is met Use MCM criteria if: 1. validation was marginally pass and you are just starting production, or 2. routine test for the previous batch was MCM, or 3. routine tests for the previous patch started as SCM, but had to go to MCM to pass	clarity